Warfarin Versus Novel Oral Anticoagulants: How to Choose?

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How to Choose?

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Anticoagulants (commonly called blood thinners) are medications that interact with the body's natural blood-clotting system to treat and prevent abnormal blood clots. Anticoagulants are used in patients who have blood clots in the legs (called deep vein thrombosis or DVT) or in the lungs (called pulmonary embolism or PE), other types of blood clots in the arteries or veins, an irregular heart rhythm called atrial fibrillation that increases the risk of stroke, and mechanical heart valves. For decades, warfarin (also known as Coumadin) was the primary anticoagulant used. Recently, several other medications known as novel oral anticoagulants (NOACs) have been studied and released on the market as alternatives to warfarin. Given the number of choices now available for patients who need anticoagulants, the benefits, risks, side effects, and convenience of each anticoagulant must be carefully considered.

How Do NOACs Differ From Warfarin?

Warfarin treats and prevents blood clots by decreasing the production of several clotting proteins that rely on vitamin K. Warfarin is taken by mouth once daily, and the dose varies depending on inherited factors, reason for the medication, and diet (Table 1). Because of the variations in doses needed for each patient, warfarin requires frequent laboratory monitoring and dose adjustment to maintain blood levels within the target range (called the international normalized ratio or INR). Below target blood levels, patients have an increased risk of clotting. Above target blood levels, the risk of bleeding increases. As with all anticoagulants, warfarin use increases the risk of bleeding. If this happens, vitamin K or various blood products can be given to replace the clotting factors affected by warfarin.

NOACs work by targeting individual clotting proteins. They do not require laboratory monitoring or dose adjustment because they reach predictable levels in most patients (Table 1). They are also shorter-acting than warfarin. If a dose of warfarin is missed, a patient's blood may still be adequately thinned because it takes several days for the anticoagulant effect to wear off. In contrast, if a dose of a NOAC is missed, patients quickly lose the anticoagulant effect and are unprotected from blood clots. Unlike warfarin, no specific antidotes are currently available to reverse the blood-thinning effect of NOACs in patients who are bleeding. Because its anticoagulant effect lasts for days, warfarin must be stopped several days before surgery and certain other procedures. During interruption of warfarin treatment, patients may need to give themselves injections with shorter-acting anticoagulants or be admitted to the hospital for intravenous anticoagulants to prevent blood clots (often called bridging). The NOACs rarely require bridging because they are shorter acting and can be safely stopped a day or two before surgery or procedures.

NOACs are taken once or twice daily (depending on the NOAC being used and the condition being treated). Although NOACs have been evaluated for stroke prevention in atrial fibrillation and treatment and prevention of DVTs and PEs, they are contraindicated for treatment in patients with mechanical heart valves.

Warfarin

Warfarin has been used for decades to treat patients with atrial fibrillation,

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Table 1. Features of Warfarin Versus NOACs

	Warfarin	NOACs
Onset of action	Slow	Rapid
Dosing	Variable	Fixed
Food interactions	Yes	No
Drug interactions	Many	Few
Routine laboratory monitoring	Yes	No
Duration of blood-thinning effect	Long	Short
Reversal agent available	Yes	No
Cost	$	$$$

NOAC indicates novel oral anticoagulant.

DVT, or PE, and mechanical heart valves. Warfarin is most commonly dosed to a target INR range of 2 to 3. It is inexpensive relative to other anticoagulant options (a month's supply costs ≈ $4). NOACs are more expensive than warfarin.

A number of challenges are associated with the use of warfarin. First, warfarin takes several days to reach target blood levels. As a result, patients often need an intravenous or injectable anticoagulant to provide adequate blood thinning while warfarin becomes effective. Patients often experience fluctuations in the INR that require dose adjustment and more frequent laboratory monitoring. Although elevated INR levels are associated with increased risk of bleeding, in particular, bleeding in and around the brain, bleeding events can occur even when the INR is within the target range. Certain foods that contain large amounts of vitamin K (such as dark green leafy vegetables including spinach, brussel sprouts, and kale) can lower the INR, whereas certain medications (including many antibiotics) can increase the INR. Because there are hundreds of potential drug interactions with warfarin, patients need to inform their healthcare providers about any medication changes. Anticoagulation Management Services (commonly called Coumadin Clinics) and home INR monitors help overcome many of the challenges of warfarin therapy.

Dabigatran

Dabigatran (Pradaxa) was the first NOAC to be released into the US marketplace. In patients with atrial fibrillation, dabigatran is better than warfarin at preventing stroke and lowered the risk of bleeding in and around the brain (one of the most dangerous complications of anticoagulants). In comparison with warfarin, dabigatran is similarly effective for the treatment of DVT and PE. Dabigatran is approved by the US Food and Drug Administration (FDA) for stroke prevention in atrial fibrillation, treatment of acute DVT or PE, and extended treatment to prevent recurrent DVT and PE. The dose of dabigatran is 150 mg twice daily. Because the kidneys eliminate dabigatran from the body, poor kidney function can result in higher levels of dabigatran and increased bleeding risk. Therefore, for stroke prevention in atrial fibrillation, the FDA approved a reduced kidney dose of dabigatran, provided in a 75-mg capsule taken twice daily.

Rivaroxaban

For stroke prevention in atrial fibrillation, rivaroxaban (Xarelto) is similarly effective in comparison with warfarin but reduces the risk of bleeding in and around the brain. Rivaroxaban is similarly effective in comparison with warfarin for treatment and prevention of DVT and PE but reduces the risk of serious bleeding complications. It is administered once or twice daily by mouth. It is FDA-approved for both stroke prevention in atrial fibrillation and treatment and prevention of DVT and PE. For stroke prevention in atrial fibrillation, a lower dose is FDA approved for patients with chronic kidney disease.

Apixaban

For patients at risk for stroke due to atrial fibrillation, twice-daily apixaban (Eliquis) is better than warfarin in the prevention of stroke. It is similarly effective in comparison with warfarin for the treatment and long-term prevention of DVT and PE. In contrast to warfarin, however, it results in fewer serious bleeding complications. Apixaban is FDA-approved for stroke prevention in patients with atrial fibrillation. Of all the NOACs, apixaban is least cleared by the kidneys and mostly metabolized by the liver.

Edoxaban

In comparison with warfarin, once-daily edoxaban is similarly effective for stroke prevention in atrial fibrillation and for treatment of DVT and PE. Edoxaban has a lower risk of serious bleeding complications than warfarin.

NOACs and Mechanical Heart Valves

Mechanical heart valves increase the risk of blood clots, including stroke. Patients with mechanical heart valves are prescribed anticoagulants (typically warfarin) to prevent blood clot formation on the valve. Whereas few studies have evaluated NOACs for this indication, 1 study showed that dabigatran was less effective and caused more bleeding than warfarin in patients with mechanical heart valves.

How to Choose?

For the first time in decades, there are now multiple anticoagulant choices for the treatment and long-term prevention of DVT and PE and the prevention of stroke in atrial fibrillation. Choosing an anticoagulant has become a challenge for patients and their healthcare providers. For some patients, the NOACs are more appealing than warfarin because of their similar or improved effectiveness and enhanced safety (Table 2). Others place a premium on the established decades-long track record of warfarin over the relatively limited experience with NOACs. Guidelines from major European medical societies recommend NOACs as the best anticoagulant option for stroke prevention in atrial fibrillation. American guidelines endorse NOACs in preference to warfarin for patients who have difficulties maintaining an INR within the desired target range. Whereas reversal agents exist for warfarin, specific antidotes have not yet been fully developed and evaluated for NOACs.

Table 2. NOACs Versus Warfarin for Stroke Prevention in Atrial Fibrillation and Treatment of DVT and PE

	Stroke Prevention in Atrial Fibrillation		Treatment of DVT/PE	
NOAC	Prevention of Stroke vs Warfarin	Major Bleeding vs Warfarin	Prevention of Recurrent DVT/PE vs Warfarin	Major Bleeding vs Warfarin in DVT/PE
Dabigatran	↓	↔	↔	↔
Rivaroxaban	↔	↔	↔	↓
Apixaban	↓	↓	↔	↓
Edoxaban	↔	↓	↔	↓

DVT indicates deep vein thrombosis; NOAC, novel oral anticoagulant; and PE, pulmonary embolism.

Medication adherence is also an important consideration. Patients who forget doses may benefit from warfarin therapy because of its longer blood-thinning effect and the common use of Anticoagulation Management Services, which provide frequent reminders about medication adherence and follow-up with INR tests. Patient convenience should also be considered, because NOACs do not require laboratory monitoring or dose adjustment and interact minimally with foods and other medications. Finally, the increased cost of NOACs in comparison with warfarin must also be considered to ensure medication access and adherence. Many manufacturers of NOACs have assistance programs to help diminish the patient cost of these medications.

Overall, healthcare providers will help patients understand the advantages and disadvantages of the different anticoagulant options. Once the options have been reviewed, patient and provider preference guide the decision making.

Further Information

For additional information, please consult the following resources:

- North American Thrombosis Forum (www.natfonline.org)
- National Blood Clot Alliance: Stop The Clot (http://www.stoptheclot.org/)
- European Society of Cardiology Guidelines for the Management of Atrial Fibrillation (http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines_focused_update_atrial_fib_ft.pdf)
- American Heart Association (http://www.heart.org/HEARTORG/)

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